

Genetics of cardiovascular and renal complications in diabetes

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ABSTRACT

The development of debilitating complications represents a major healthcare burden associated with the treatment of diabetes. Despite advances in new therapies for controlling hyperglycemia, the burden associated with diabetic complications remains high, especially in relation to cardiovascular and renal complications. Furthermore, an increasing proportion of patients develop type 2 diabetes at a younger age, putting them at higher risk of developing complications as a result of the increased exposure to hyperglycemia. Diabetes has become the main contributing cause to end-stage renal disease in most countries. Although there has been important breakthroughs in our understanding of the genetics of type 1 and type 2 diabetes, bringing important insights towards the pathogenesis of diabetes, there has been comparatively less progress in our understanding of the genetic basis of diabetic complications. Genome-wide association studies are beginning to expand our understanding of the genetic architecture relating to diabetic complications. Improved understanding of the genetic basis of diabetic cardiorenal complications might provide an opportunity for improved risk prediction, as well as the development of new therapies.

INTRODUCTION

The past few decades have seen a marked increase in the prevalence of diabetes, with most regions of the world affected by this global epidemic. It has been estimated that the number of people affected by diabetes was approximately 382 million in 2013, and is estimated to increase further to 592 million by 2035, with close to 50% residing in Asia and the Western Pacific region^{1–3}. Furthermore, there is an increasing proportion of young individuals being diagnosed with diabetes. In the Joint Asia Diabetes Evaluation Program, approximately 20% of patients with diabetes in Asia were diagnosed before the age of 40 years⁴. Diabetes is associated with the development of a variety of microvascular complications including retinopathy, nephropathy and neuropathy, but also macrovascular complications including coronary heart disease, stroke and peripheral vascular disease. In addition to vascular complications, diabetes is also associated with other comorbidities, including increased risk of different malignancies, osteoporosis, depression, sleep apnoea and reproductive disorders. Among the different complications associated with diabetes, cardiovascular and renal complications account for a major burden of healthcare costs

associated with diabetes. For example, it has been estimated that annual hospital costs for patients with uncomplicated type 2 diabetes in Asia average approximately 76 international dollars, compared with more than 1,800 international dollars for a patient complicated by a coronary event⁵. Coronary events, cerebrovascular events, heart failure, nephropathy and peripheral vascular disease account for 60% of overall hospital use among patients with type 2 diabetes in Asia⁵. Importantly, the development of microvascular and macrovascular complications differ somewhat. While diabetic retinopathy and diabetic nephropathy tend to develop after the onset of diabetes, the risk of macrovascular complications, such as coronary heart disease (CHD), might be present before the diagnosis of diabetes, partly driven by the underlying insulin resistance and coexisting cardiometabolic risk factors⁶. It has been highlighted that patients with young-onset diabetes, with longer exposure to diabetes with time, are at high risk of vascular complications⁷ and end-stage renal disease (ESRD)⁸. In Hong Kong Chinese, it was shown that patients with young-onset diabetes before the age of 40 years were at a substantially higher risk of cardiorenal complications when compared with patients with onset after the age of 40 years, with the risk mainly attributed to the longer disease duration⁹. The current situation of increasing young-onset diabetes is therefore likely to translate to further

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escalation of the number of people affected by diabetic complications. Identifications of biomarkers, such as genetic factors, might help to identify individuals at risk of diabetic complications, and could also help to shed new light on the pathogenesis of diabetic complications. In the present article, an overview of the current state of knowledge regarding recent advances in research on genetic factors for diabetic complications, in particular, cardiovascular and renal complications, is presented.

PATHOGENESIS OF DIABETIC VASCULAR COMPLICATIONS

Several pathways are known to be implicated in the pathogenesis of diabetic vascular complications. These include activation of the protein kinase C pathway, formation of glycation end-products and accumulation of sorbitol through the aldose reductase pathway^{10,11}. A unifying hypothesis has been proposed, with generation of reactive oxygen species as the key central theme linking these different pathogenetic mechanisms¹². In addition to these key pathways, which are activated by hyperglycemia, there are other important mechanisms implicated in the development of diabetic complications, including, for example, in relation to coexisting hypertension and hyperlipidemia, activation of the renin–angiotensin system, adipokines production, protein folding and post-translational modifications, such as O-Glc-Nac modifications, inflammation and growth factors (Figure 1)^{11,13}.

While the development of macrovascular complications shares similarities with those of microvascular complications, there are also important differences. Although hyperglycemia is an important mediator of endothelial dysfunction, one of the earliest manifestations for vascular dysfunction, macrovascular complications have insulin resistance, loss of insulin signaling and progression of atherosclerosis as the central processes that drive pathology¹⁴. Hence, traditional risk factors for atherosclerosis, including smoking, elevated blood pressure, elevated low-density lipoprotein cholesterol as well as the mixed dyslipidemia classically present in a diabetic state, all play a prominent role in the development of coronary artery disease in diabetes, with elevated glucose playing an important, but perhaps, less significant role¹⁵. This is supported by experience from clinical trials, which noted that the cardioprotective effect through intensive glucose-lowering is comparatively modest¹⁶, in contrast to the dramatic effects of normoglycemia in reducing diabetic microvascular complications, highlighting the central role of hyperglycemia in the pathogenesis of diabetic microvascular complications, such as diabetic retinopathy, with hypertension and dyslipidemia being additional risk factors that accelerate this process^{17,18}.

In addition to pathways activated by hyperglycemia, recent studies have highlighted the importance of endogenous protective pathways that could protect against the development of diabetic vascular complications¹⁴. These protective factors include

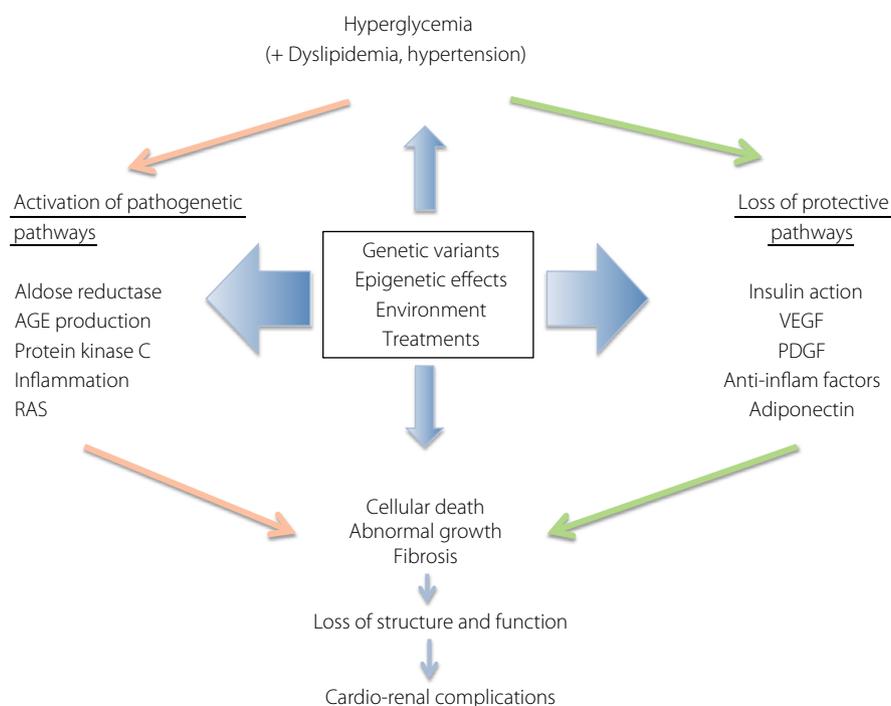


Figure 1 | The key role of genetics and epigenetics in modulating the pathogenesis of diabetic cardiovascular and renal complications. Although hyperglycemia is the hallmark metabolic abnormality in type 1 diabetes, the metabolic milieu in type 2 diabetes is characterized by hyperglycemia and insulin resistance, often with coexisting hyperlipidemia and hypertension. AGE, advanced glycation end-products; PDGF, platelet-derived growth factor; RAS, renin–angiotensin system; VEGF, vascular endothelial growth factor.

insulin, platelet-derived growth factor, vascular endothelial growth factor and activated protein C, which could provide new candidate genes for studying genetic factors protective against diabetic complications, as well as being targets for potential therapies to reduce diabetic vascular complications (Figure 1).

HERITABILITY OF DIABETIC COMPLICATIONS AND APPROACHES TO IDENTIFY GENETIC FACTORS FOR DIABETIC COMPLICATIONS

Several lines of evidence suggest that genetic factors might be implicated in the development of diabetic microvascular, as well as macrovascular, complications. In the Diabetes Control and Complications Trial, the risk of severe retinopathy was fourfold higher among relatives of retinopathy-positive patients versus subjects without retinopathy, suggesting familial clustering and a possible role of genetic factors¹⁹. Subsequent studies estimated the heritability for diabetic retinopathy to vary between 18–27% for any diabetic retinopathy, and up to 25–52% for proliferative diabetic retinopathy in either type 1 or type 2 diabetes²⁰. The heritability of diabetic nephropathy is generally believed to be higher than that of diabetic retinopathy, and has been reported to range from 0.3 to 0.75 in different studies²¹, with one study reporting heritability of albuminuria and glomerular filtration rate in type 2 diabetes of 0.46 and 0.75, respectively, after adjustment of covariates including blood pressure and glycated hemoglobin²¹.

An estimate of heritability for ischemic heart disease in diabetes is approximately 50%²², whereas a heritability estimate of carotid intima-medial thickness, a well-validated marker of sub-clinical atherosclerosis, was reported to be 0.41 in type 2 diabetes²³. Collectively, these and earlier studies support a role for genetic factors in the pathogenesis of both diabetic microvascular and macrovascular complications, and the rationale to search for such genetic factors.

Strategies to search for genetic susceptibility factors for common complex diseases, such as type 2 diabetes and diabetic complications, have evolved over the years with improved molecular technology as well as better understanding of the genetic architecture. Earlier studies mainly utilized linkage analysis in families with clustering of cases, and examined the cosegregation of parts of the genome (marked by microsatellite markers) with the disease of interest (e.g., diabetic complications). Identification of linked loci found through linkage analysis is usually followed up by fine-mapping of the confirmed loci and examining candidate genes within the linked region in functional studies. More recently, microsatellite markers have been replaced with dense genotyping arrays consisting of hundreds of thousands of single nucleotide polymorphisms (SNPs), which are common genetic variants located across the entire genome. These genotyping arrays were designed by leveraging on knowledge of the genetic architecture of the human genome gained through the HapMap project, which identified a subset of SNPs that would capture most of the genetic variation in the different major populations.

Association studies are powerful ways to identify genetic variants associated with diabetic complications. Earlier candidate gene studies rely on prior knowledge and understanding of the pathogenesis of diabetic complications to look for an association between genetic variants in genes implicated in these pathways and the presence of diabetic complications. Although a large number of candidate-gene association studies have been published, many of these studies have been plagued by the relative lack of replication for the reported association. More recently, publication of the HapMap and advances in the manufacturing of genotyping arrays have made possible a hypothesis-free approach utilizing genome-wide association studies (GWAS). GWAS have been highly successful in identification of common genetic variants for complex diseases, and in the case of type 2 diabetes, have led to identification of over 100 genetic variants²⁴. As will be discussed in later sections, this approach is now also beginning to bear fruit on the search for genetic factors for diabetic complications. There are also ongoing studies using other technologies, such as next-generation sequencing, and the relative merits of the different techniques in the discovery process will partly depend on the frequency and effect size of the risk alleles being sought (Figure 2).

Although there will be some overlap in the genetic factors associated with complications in type 1 and type 2 diabetes, as shown in the subsequent section on diabetic kidney complications, there are also likely to be important differences given the different metabolic environment associated with type 1 and type 2 diabetes (Figure 1). Hence, for the purpose of the present review, genetic factors associated with diabetic complications will be presented and discussed in relation to type 1 diabetes and type 2 diabetes separately.

GENETICS OF CARDIOVASCULAR COMPLICATIONS IN DIABETES

Patients with diabetes have an approximately two- to fourfold increased risk of coronary heart disease⁶. In a recent meta-analysis, the association between diabetes and incident cardiovascular disease was most notable for peripheral artery disease, ischemic stroke, stable angina, heart failure and coronary heart disease²⁵. In the United Kingdom Prospective Diabetes Study, clinical risk factors associated with the development of CHD in diabetes were elevated low-density lipoprotein cholesterol, reduced high-density lipoprotein (HDL) cholesterol, elevated triglyceride, glycated hemoglobin, systolic blood pressure, fasting blood glucose and smoking¹⁵. In studies from Asia, the major predictors of CHD in diabetes among Hong Kong Chinese were increasing age, male sex, smoking status, duration of diabetes, lowered estimated glomerular filtration rate (eGFR), increasing albuminuria and non-HDL cholesterol²⁶. In the Japanese Diabetes Complications Study, the main predictors for cardiovascular complications among patients with type 2 diabetes were identified as non-HDL cholesterol, total cholesterol/HDL-cholesterol ratio and low-density lipoprotein cholesterol²⁷, and elevated

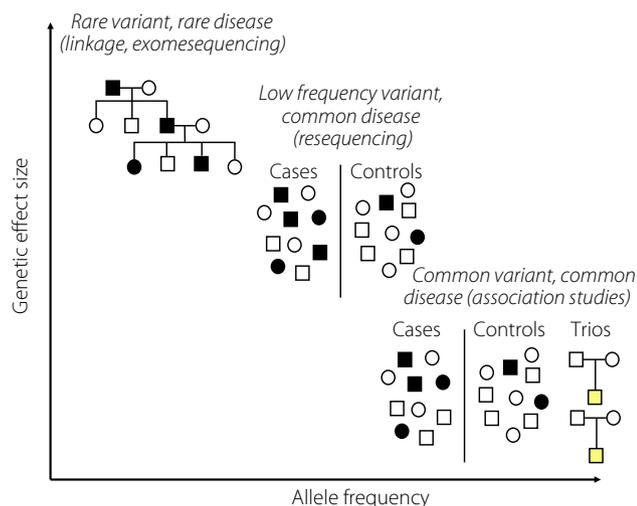


Figure 2 | Different strategies to identify genetic factors for diseases. Linkage analyses in families are traditionally used to identify genetic mutations with large effects (Mendelian forms of monogenic diseases). This strategy has now been replaced by the use of exome sequencing. For low-frequency genetic variants (allele frequency ranging from 0.03 to 5% of population) with moderate effect, resequencing approaches are currently being utilized. For the majority of common genetic risk variants (minor allele frequency 5% or more) underlying common polygenic diseases, such as type 2 diabetes, the effect size of the risk variant is small (typically with odds ratio 1.1–1.8), and have been identified through large-scale association studies and genome-wide association studies. In addition, association studies in large cohorts or trios have aided the identification of common variants associated with quantitative traits, such as estimated glomerular filtration rate.

triglyceride was noted to be a particularly important risk factor for incident CHD²⁸.

Although hyperglycemia plays an important role in the development of vascular complications in patients with both type 1 and type 2 diabetes, recent insights from clinical trials suggest a different risk–benefit ratio with regard to the role of intensive glucose lowering and the prevention of cardiovascular complications. In the Diabetes Control and Complications Trial/Epidemiology of Diabetic Interventions and Complications study carried out in patients with type 1 diabetes mellitus, intensive glucose lowering was associated with a reduction in cardiovascular events in the post-trial follow-up period²⁹. Meta-analysis of glucose-lowering trials in type 2 diabetes suggested a small reduction in CHD with intensive glucose lowering¹⁶, and the beneficial effects of glucose lowering on CHD might only emerge after a prolonged period of follow up³⁰. Recent data from the Look AHEAD Trial, whereby participants were randomized to the intensive lifestyle intervention group had 31% lower incidence of chronic kidney disease (CKD), but no reduction in CHD, suggest that although strategies to reduce cardiometabolic risk factors are important, the benefit in reducing cardiovascular complications could take a long time to occur^{31,32}. Multidisciplinary approaches targeting multiple car-

diometabolic risk factors have been shown to reduce the development of cardiovascular complications³³. Hence, early identification of at-risk individuals and implementation of early multifactorial risk factors management might be required to reduce the burden associated with CHD in diabetes.

Genetic Factors for CHD in Type 1 Diabetes

There are relatively few studies that have investigated the role of genetic factors in the development of CHD in type 1 diabetes. An early study that investigated the role of two functional polymorphisms in the promoter of the *RAGE* gene (–429T/C and –374 T/A) and one in the advanced glycation end-products binding domain (G82S) in 996 Finnish type 1 diabetic patients noted a reduced risk of coronary heart disease and myocardial infarction, as well as peripheral vascular disease in patients with the AA genotype of the –374 T/A polymorphism compared with those with the TT+ TA genotype³⁴. Another candidate gene study that examined the roles of genetic variants in the renin–angiotensin system found that carriers of the TT genotype at the angiotensinogen (*AGT*) gene M235T polymorphism, the insertion/deletion (I/D) polymorphism at the angiotensin converting enzyme (*ACE*) gene and AA/AC genotype at the angiotensin type 1 receptor are at a significantly higher risk of progression of coronary artery calcification³⁵. These are some examples of the earlier studies that explored the genetic factors for CHD in type 1 diabetes. There are now ongoing efforts to utilize GWAS to advance the understanding of genetic factors underlying CHD in type 1 diabetes.

Genetic Factors for CHD in Type 2 Diabetes

Linkage Studies

Previous linkage studies have identified a few linkage regions for cardiovascular disease-related traits in type 2 diabetes, including linkage signal in the chromosome 19q region with elevated triglyceride levels³⁶ and total cholesterol³⁷. In the Diabetes Heart Study, linkage of a locus on chromosome 3 with CVD in type 2 diabetes was noted³⁸.

Candidate Gene Studies

Several studies have examined variants in pathways implicated in insulin resistance, inflammation and development of vascular complications, and the association with the risk of cardiovascular complications in diabetes. Of particular note is the large number of studies carried out in relation to the renin–angiotensin system and the adiponectin pathway. The D allele of the *ACE* gene was first shown to be associated with increased risk of CHD in type 2 diabetes back in 1994³⁹, with several studies also supporting this association, though a study in Chinese did not observe an association between the D allele and later risk of CHD in a prospective cohort⁴⁰. Adiponectin is an adipokine secreted by adipocytes that has anti-atherogenic effects, and is believed to be an important link between obesity and cardiovascular diseases⁴¹. In a meta-analysis including four studies, with 827 type 2 diabetes cases with CVD and 1,887

CVD-free control participants, the +276T homozygote was significantly associated with a 45% reduction in the risk of CVD⁴². Several studies have examined the role of the peroxisome proliferator-activator receptor gamma Pro12Ala polymorphism and CHD risk, though the results appear inconclusive^{43–45}. In a candidate gene-based study of genes for inflammation, thrombosis, vascular tone and lipid metabolism in a prospective cohort of Chinese patients with type 2 diabetes, variants in *SCYA11* (eotaxin), *PON2* (paroxonase 2) and *ADRB3* (β_3 -adrenergic receptor) were independently associated with incident cardiac events including CHD and/or heart failure⁴⁶.

Insights from GWAS for CHD

Recent GWAS have identified more than 40 variants associated with coronary artery disease^{47,48}. Among these, several regions appear to harbor variants that are also associated with type 2 diabetes⁴⁹. For example, in the chromosome 9p21 region identified to be associated with CHD⁵⁰, the cell cycle genes *CDKN2A* and *CDKN2B* have also been implicated in a GWAS for type 2 diabetes^{51–53}. In fact, in a genome search meta-analysis to look for shared genetic susceptibility between type 2 diabetes, CHD and obesity, two loci in the 9p21.1-a21.32 region were identified to be shared by type 2 diabetes, CHD and obesity⁴⁹. Other genetic factors associated with CHD in the general population, such as variants in *PCSK9*, have also been found to be associated with CHD in type 2 diabetes⁵⁴.

Early replication studies of these GWAS-identified variants for CHD have suggested heterogeneity in genetic effects among individuals with or without diabetes. For example, it has been suggested that variants at the 9p21 locus have a larger effect on the risk of CHD in patients with type 2 diabetes (compared with subjects without diabetes), particularly showing an interaction with poor glycemic control⁵⁵. Furthermore, in a study in type 2 diabetes patients of variants associated with CHD (in non-diabetic individuals), just five out of 15 variants from 12 loci were found to show consistent association with CHD in type 2 diabetes. A genetic risk score (GRS) ≥ 8 composed of risk variants at rs4977574 (*CDKN2A/2B*), rs12526453 (*PHACTR1*), rs646776 (*CELSR2-PSRC1-SORT1*), rs2259816 (*HNF1A*) and rs11206510 (*PCSK9*) was associated with twofold increase in the risk of CHD in type 2 diabetes⁵⁴. Another recent study that examined a GRS consisting of 13 or 30 SNPs identified from GWAS for CHD in the general population noted an association between GRS score and prior cardiovascular disease, coronary artery calcification, and cardiovascular mortality in a cohort predominantly of African American descent⁵⁶. Nevertheless, a comparison of the area under the curve for prediction or use of a net reclassification index using genetic variants suggested that including genetic variants did not improve prediction of cardiovascular risk above that of traditional clinical risk factors⁵⁶. A study that examined SNPs associated with HDL cholesterol levels did not detect an association between GRS and the risk of cardiovascular mortality in type 2 diabetes⁵⁷.

GWAS for CHD in Type 2 Diabetes

In the first GWAS of CHD in type 2 diabetes, a total of 1,517 CHD and 2,671 CHD-negative controls with type 2 diabetes were included in a three-stage genome-wide analysis, including subjects from the Nurses' Health Study and Health Professionals Follow-up Study, the Joslin Heart Study and the Gargano Heart Study. One variant, rs10911021, showed a significant association in all three stages and showed genome-wide significance when all three stages were combined, with combined odds ratio (OR) 1.36 (95% confidence interval [CI] 1.22–1.51)⁵⁸. Interestingly, no association was found between rs10911021 and CHD for 737 non-diabetic CHD cases and 1,637 non-diabetic CHD-negative controls. This was consistent with results of the interaction analysis, suggesting that the association between this variant and CHD appeared specific for type 2 diabetes patients. Furthermore, among 22,233 CHD cases and 64,762 controls from the general population included in the Coronary ARtery DIsease Genome-Wide Replication and Meta-Analysis (CARDIoGRAM) Study, this variant showed only a nominal significant association with CHD (OR 1.04, 95% CI 1.01–1.07, $P = 0.01$), likely representing an association driven by the small proportion of patients with type 2 diabetes included in CARDIoGRAM⁵⁸. The variant was not associated with the risk of type 2 diabetes or insulin resistance, but instead was associated with plasma markers of glutamic acid metabolism and the γ -glutamyl cycle, thereby providing novel insights into the pathogenesis of CHD in patients with type 2 diabetes. Whether this variant is also associated with the risk of CHD in type 1 diabetes mellitus remains to be established.

Several important insights have emerged from these studies. They highlighted some important differences in the genetic factors associated with risk of CHD in patients with diabetes compared with the general population, although there is some important overlap. Therefore, there is the need to carry out studies to identify susceptibility genes for CHD specifically among patients with type 2 diabetes in order to identify susceptibility factors in diabetes, given the heterogeneity of effects when compared with studies carried out in non-diabetic individuals.

GENETICS OF RENAL COMPLICATIONS IN DIABETES

Diabetes is the major cause of ESRD and need for dialysis in most developed countries. The clinical risk factors that are associated with development and progression of renal complications depend on the precise definition of the renal complications, but typically include increasing duration of diabetes, poor glycemic control, elevated blood pressure, dyslipidemia and other cardiometabolic risk factors, as well as smoking. Most earlier studies on genetic factors for diabetic kidney complications have focused on albuminuria as a phenotypic trait, and diabetic nephropathy is most often defined as the development of significant albuminuria, of ≥ 300 mg/24 h, for both type 1 and type 2 diabetes. Over recent years, with increasing popularity of estimated eGFR for defining chronic kidney disease, more

studies have utilized the presence of CKD among diabetes patients as a clinical end-point for diabetic kidney complications, or diabetic kidney disease. A more severe phenotype, ESRD, defined as eGFR <15 mL/kg/m², or the need for dialysis or renal transplantation, is a more consistent phenotype and usually also invariably associated with significant proteinuria. Some genetic studies have also defined a renal phenotype based on worsening of proteinuria or significant worsening of renal function, although in analysis it is important to note that albuminuria as a quantitative trait can be readily modified by the concomitant administration of ACE inhibitors and angiotensin receptor blockers, as well as other potentially nephroprotective agents.

Link between Renal and Cardiovascular Complications

It is well established that there is a close link between coronary heart disease and renal dysfunction^{59,60}. Meta-analysis of studies suggests that reduced eGFR rate and increased albuminuria have an independent and multiplicative effect on cardiovascular mortality^{60,61}, and this relationship is similar in individuals with or without diabetes⁶². In a cohort of 2,434 Chinese patients with type 2 diabetes, elevated serum creatinine, eGFR <60 mL/min and urine albumin/creatinine ratio (ACR) >30 mg/g were independent risk factors for coronary artery disease⁶³. In a study utilizing nationally representative cohorts from Taiwan, the synergistic effects of diabetes and ESRD in modifying the risk of cardiovascular complications was shown, with diabetes and ESRD associated with twofold and fourfold increased risk of acute myocardial infarction, respectively, but the presence of both is associated with an almost 12-fold increased risk for acute myocardial infarction⁶⁴. This link between CHD and CKD is partly due to a sharing of predisposing risk factors. In addition to hypertension, other metabolic syndrome traits, such as central obesity and hypertriglyceridemia, have also been identified to predict the risk of incident CKD among patients with type 2 diabetes⁶⁵. Integrated management of multiple risk factors has been emphasized for the management of patients with diabetes and renal disease^{66,67}. In addition to an overlap of predisposing clinical risk factors, it is possible that the two conditions could also have shared genetic factors (akin to the scenario seen in type 2 diabetes and CHD), though these have yet to be discovered (Figure 3).

Type 1 Diabetes and Diabetic Nephropathy

The important role of genetic factors in the pathogenesis of diabetic kidney complications was first highlighted by studies by Seaquist *et al.*⁶⁸, who noted that 83% of diabetic siblings of probands with type 1 diabetes and nephropathy had nephropathy themselves, compared with just 17% of patients with type 1 diabetes without nephropathy. Similar familial clustering has been observed in studies of diabetic nephropathy in type 2 diabetes, and estimates of heritability of albuminuria have ranged from 0.3 to 0.44, with similar heritability of 0.6–0.75 for renal traits, such as glomerular filtration rate⁶⁹.

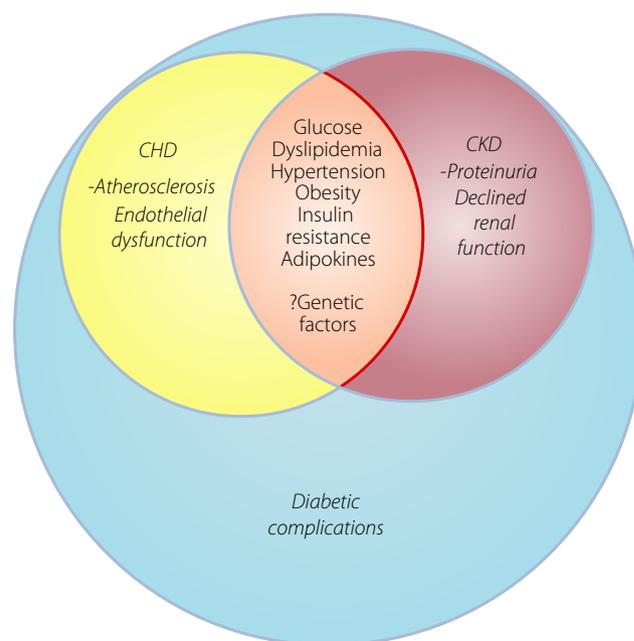


Figure 3 | The interlinked relationship and overlap between cardiovascular and renal complications in diabetes. In addition to shared risk factors, there might be potentially shared genetic factors that predispose to the development of cardiovascular as well as renal complications in diabetes. CHD, coronary heart disease; CKD, chronic kidney disease.

Candidate Gene Studies

A large number of studies have utilized the candidate gene approach to examine the association with diabetic nephropathy. The results from some of these studies are summarized in Table 1. Although several of these showed a suggestive association, only a few genetic variants have been confirmed to be associated with diabetic nephropathy in type 1 or type 2 diabetes through large-scale meta-analyses. For example, in a meta-analysis including 14,727 participants from 47 studies, carriers of the II insertion/deletion polymorphism at the *ACE* gene were found to have approximately 22% lower risk of diabetic nephropathy in both type 1 and type 2 diabetes, with the protective effect most marked among Asians patients⁷⁰. An updated meta-analysis with 26,580 participants from 63 studies confirmed this earlier observation, again noting the greater protective effect of the II polymorphism among Asians⁷¹. Furthermore, carriers of the I allele also appear to derive greater renoprotection from ACE inhibition⁷².

Findings from GWAS of Diabetic Nephropathy in Type 1 Diabetes

The Genetics of Kidney in Diabetes study was the first successful example of identifying susceptibility loci using the GWAS approach. This study included 820 case subjects (including 284 type 1 diabetes with proteinuria and 536 with ESRD) and 885 controls (type 1 diabetes >15 years with normoalbuminuria), and identified risk variants near two regions, *FRMD3* (FERM

Table 1 | Summary of genetic variants for diabetic vascular complications

DM complications	Phenotype	Study type	Ethnic group	Polymorphism	Candidate gene/nearest gene	Chrom location	References
<i>CV complications</i>							
Type 2 diabetes mellitus	CHD	Candidate gene	Multi-ethnic	+G276T	Adiponectin	3q27	Qi <i>et al.</i> , Diabetes (2006)
		Candidate gene	European	rs4977543	CDKN2A/2B	9p21	Qi <i>et al.</i> , JACC (2011)
		Candidate gene	European	rs12526453	PHACTR1	6p24	Qi <i>et al.</i> , JACC (2011)
		Candidate gene	European	rs646776	CELSR2-PSRC1-SORT1	1p21	Qi <i>et al.</i> , JACC (2011)
		Candidate gene	European	rs2259816	HNF1A	12q24	Qi <i>et al.</i> , JACC (2011)
CHD	GWAS	Candidate gene	European	rs11206510	PCSK9	1p32	Qi <i>et al.</i> , JACC (2011)
		Candidate gene	European	rs2383206	CDKN2A/2B	9p21	Doria <i>et al.</i> , JAMA (2008)
		Candidate gene	European	rs10911021	GLUL	1q25	Qi <i>et al.</i> , JAMA (2013)
<i>Kidney complications</i>							
Type 1 diabetes mellitus	Nephropathy	Candidate gene	European	rs1805101 (K121Q)	ENPP1	6q22-23	Canani <i>et al.</i> , Diabetes (2002)
		Candidate gene	European	rs4344	ACE	17q23	Wang <i>et al.</i> , J Renin Angiotensin Aldosterone Syst (2012)
Nephropathy	GWAS	Candidate gene	European	374T/A	RAGE	6p21	Lindholm <i>et al.</i> , Diabetologia (2006)
		Candidate gene	European	rs13293564	UNC13B	9p13	Tregouet <i>et al.</i> , Diabetes (2008)
		Candidate gene	European	rs1617640	EPO	7q22	Williams <i>et al.</i> , Diabetes (2012)
		Replication	European	rs11769039	ELMO1	7p14	Perzolesi <i>et al.</i> , Diabetes (2009)
		Candidate gene	European	rs1888747	FRMD3	9q21	Perzolesi <i>et al.</i> , Diabetes (2009)
		Candidate gene	European	rs13289150	FRMD3	9q21	Perzolesi <i>et al.</i> , Diabetes (2009)
		Candidate gene	European	rs451041	CARS	11p15	Perzolesi <i>et al.</i> , Diabetes (2009)
		Candidate gene	European	rs39075	CPVL/CHN2	7p	Perzolesi <i>et al.</i> , Diabetes (2009)
		Candidate gene	European	rs1411766	SORBS1	13q	Perzolesi <i>et al.</i> , Diabetes (2009)
		Candidate gene	European	rs1326934	ENPP1	10q24	Germain <i>et al.</i> , Diabetologia (2015)
ESRD	ESRD/proteinuria	Candidate gene	European	rs1805101	ENPP1	6q22-23	Canani <i>et al.</i> , Diabetes (2002)
		Candidate gene	European	rs7583877	AFF3	2q11	Sandholm <i>et al.</i> , PLoS Genetics (2012)
		Candidate gene	European	rs12437854	RGMA/MCTP2	15q	Sandholm <i>et al.</i> , PLoS Genetics (2012)
		Candidate gene	European	rs7588550	ERBB4	2q33	Sandholm <i>et al.</i> , PLoS Genetics (2012)
		Candidate gene	European	rs13447075	PVT1	8q24	Millis <i>et al.</i> , Diabetes (2007)
ESRD in type 1 diabetes mellitus	ESRD in type 1 diabetes mellitus	Candidate gene	European	rs2648862	PVT1	8q24	Millis <i>et al.</i> , Diabetes (2007)
		Replication	European	rs11769039	ELMO1	7p14	Perzolesi <i>et al.</i> , Diabetes (2009)

Table 1 (Continued)

DM complications	Phenotype	Study type	Ethnic group	Polymorphism	Candidate gene/nearest gene	Chrm location	References
Type 2 diabetes mellitus	Nephropathy	Candidate gene	Multi-ethnic	rs179975	ACE	17q23	Mooyart <i>et al.</i> , <i>Diabetologia</i> (2011)
		Candidate gene		rs4646994 rs 4344	ACE	17q23	Ng <i>et al.</i> (2005), Wang <i>et al.</i> (2012)
		Candidate gene		rs4646994	ACE	17q23	Zhong <i>et al.</i> , <i>JRAAS</i> (2015)
		Candidate gene		rs4646994	ACE	17q23	Zhong <i>et al.</i> , <i>JRAAS</i> (2015)
ESRD		Candidate gene	Multi-ethnic (incident DN)	rs759853	Aldose reductase	7q35	So <i>et al.</i> , <i>Diabetes Care</i> (2008)
				Microsatellite	Aldose reductase	7q35	So <i>et al.</i> , <i>Diabetes Care</i> (2008)
				rs1801282	APOE	19q13	Herrmann <i>et al.</i> , <i>Diabetes</i> (2002); Liu <i>et al.</i> , <i>Diabetes Care</i> (2010)
				rs2237897	PPARG	3p25	Diabetes Care (2010)
				rs2237897	KCNQ1	11p15	Ohshige <i>et al.</i> , <i>Diabetes Care</i> (2010)
				D18S880	APOE	19q13	Li <i>et al.</i> , <i>Mol Biol Rep</i> (2011)
				rs1799883	CNDP1	18q22	Janssen <i>et al.</i> , <i>Diabetes</i> (2005); Mooyart <i>et al.</i> , <i>Diabetologia</i> (2011)
				rs451041	FABP2	4q28	Canani <i>et al.</i> , <i>Diabetes</i> (2005)
				rs1411766	CARS	11p15	Pezzolesi <i>et al.</i> , <i>Kidney Int</i> (2011)
				rs1531343	HMG2A	13q	Pezzolesi <i>et al.</i> , <i>Kidney Int</i> (2011)
ESRD		Candidate gene	Multi-ethnic	rs1531343	ACE	12q24.1	Alkayali <i>et al.</i> , <i>Diabetologia</i> (2013)
				rs1411766	Near IRS2	13q	Maeda <i>et al.</i> , <i>Diabetes</i> (2010)
				Arg913Gln	SLC12A3	16q13	Tanaka <i>et al.</i> , <i>Diabetes</i> (2003)
				rs741301	ELMO1	7p14	Shimazaki <i>et al.</i> , <i>Diabetes</i> (2005)
				rs2268388	ACACB	12q24.1	Maeda <i>et al.</i> , <i>PLoS Genet</i> (2010)
				rs4646994	ACE	17q23	Yu <i>et al.</i> , <i>Nephrology</i> (2012)
				rs4646994	ACE	17q23	Yu <i>et al.</i> , <i>Nephrology</i> (2012)
				rs3760106	PRKCB1	16p11	Ma <i>et al.</i> , <i>JAMA</i> (2010)
				rs7754586	ENPP1	6q24-27	Keene <i>et al.</i> , <i>Diabetes</i> (2008)
				rs4478844	OR2AK2	1q44	Cooke Bailey <i>et al.</i> , <i>Hum Genet</i> (2014)
ESRD in type 2 diabetes mellitus		Candidate gene	African American	rs3747154	LIMK2	22q12	Cooke Bailey <i>et al.</i> , <i>Hum Genet</i> (2014)
				rs11769039	ELMO1	7p14	Leak <i>et al.</i> , <i>Ann Hum Genet</i> (2009)
				rs1345365	ELMO1	7p14	Hanson <i>et al.</i> , <i>Diabetes</i> (2007)
				rs2720709	PVT1	8q24	Hanson <i>et al.</i> , <i>Diabetes</i> (2007)
				rs2648875	PVT1	8q24	Hanson <i>et al.</i> , <i>Diabetes</i> (2007)
				Resequencing			

CHD, coronary heart disease; CV, cardiovascular; DM, diabetes mellitus; ESRD, end-stage renal disease; GWAS, genome-wide association studies.

domain-containing protein 3) and *CARS* (cysteinyl-tRNA synthetase) as being associated with nephropathy in type 1 diabetes in two different cohorts⁷³. In addition, loci near the 7p region, near *CHN2/CPVL*, and an intergenic region near chromosome 13q, also show a suggestive association with nephropathy⁷³.

More recently, collaborative efforts have led to an international consortium, the Genetics of Nephropathy: an International Effort Consortium, which includes three existing datasets for type 1 diabetes nephropathy, the All Ireland Warren 3 Genetics of Kidneys in Diabetes UK Collection, Finnish Diabetic Nephropathy Study and the Genetics of Kidneys in Diabetes US Study, with a total of 6,691 individuals in the discovery phase. The 41 top ranked SNPs were genotyped in an additional 5,873 individuals, with combined meta-analysis showing two SNPs associated with ESRD: rs7583877 in the *AFF3* gene, and an intergenic SNP on chromosome 15q, rs12437854. Functional analysis suggests that *AFF3* modulates renal fibrosis through the transforming growth factor-beta pathway. In addition, analysis using the same dataset identified an intronic SNP within the *ERBB4* gene, rs7588550, to be associated with diabetic nephropathy (defined as proteinuria or ESRD), though this did not reach genome-wide significance⁷⁴. Interestingly, in this large meta-analysis, no significant association signal was identified for the combined proteinuria/ESRD phenotype, suggesting this phenotype might have been too heterogeneous. In a recent study that examined several previously identified variants associated with nephropathy in type 1 diabetes using samples from the Genetics of Nephropathy: an International Effort Consortium, most variants were not replicated, and the effect of a previously identified erythropoietin (*EPO*) gene promoter polymorphism was attenuated. The rs179975 polymorphism at the *ACE* gene remained nominally significant⁷⁵. The study highlights the limitations of earlier smaller case-control studies, often with variable phenotypes between studies. Furthermore, it showed the need for independent replication as well as large-scale meta-analysis of available datasets.

Type 2 Diabetes and Diabetic Kidney Complications

Early Linkage Analyses and Other Studies

Early studies have identified several regions associated with diabetic nephropathy in type 1 and type 2 diabetes, including regions on chromosome 3q, 7p, 7q, 9, 10q and 18q (Table 1)^{69,76}.

The largest genome-wide linkage analysis was carried out in the Family Investigation of Nephropathy and Diabetes, which included 2,616 individuals from 1,235 pedigrees across all ethnic groups, including African Americans, South-West American Indians, European Americans and Mexican Americans. Proband had diabetes with either biopsy-proven diabetic nephropathy, ESRD attributed to diabetic nephropathy or CKD, whereas controls had diabetes of at least 10 years duration with no evidence of kidney disease, ascertained through

history, eGFR and urine ACR. Approximately 90–95% of the cohort had type 2 diabetes. Results from the Family Investigation of Nephropathy and Diabetes Study confirmed previous linkage regions and identified novel ones. Suggestive linkage was seen on chromosome 6p and 7p for diabetic nephropathy, whereas regions 3p, 7q, 16q and 22q showed evidence of linkage for ACR. There were notable differences in linkage signals across the different ethnic groups, with the major ethnic-specific linkage signals for diabetic nephropathy being chromosome 6p, 7p, 7q and 11p. The European American samples provided the greatest contribution to the linkage signal in the 6p region^{76,77}. The study also found linkage signals near several loci identified through the GWAS approach, including SNPs near the candidate region *CNDP1*.

Candidate Gene Studies

A large number of candidate gene studies have been carried out for diabetic nephropathy. These have included studies of variants in pathways implicated in the pathogenesis of diabetic nephropathy, such as the renin-angiotensin system, polyol pathway, protein kinase C pathway, AGE, oxidative stress, inflammation, angiogenesis, fibrosis and apoptosis, as well as variants in the lipid pathway^{11,78}. This has led to identification of a large number of genetic variants with suggestive association with diabetic nephropathy⁶⁹. The insertion/deletion polymorphism in the *ACE* gene has been shown to be associated with the risk of diabetic nephropathy in type 1 and type 2 diabetes^{70,71}, and was associated with incident renal end-point in a prospective cohort of Chinese patients with type 2 diabetes⁴⁰. In a study of 41 pathway-related loci associated with diabetic nephropathy, it was noted that a haplotype from *NOX4* and variants in *ET-1* were associated with diabetic nephropathy, as well as plasma Cu/Zn superoxide dismutase concentrations, suggesting the SNP might be associated with nephropathy through increased oxidative burden⁷⁹.

Another group of candidate gene studies have examined the role of genetic variants associated with type 2 diabetes to assess its role in diabetic nephropathy. For example, the Pro12Ala polymorphism of *PPARG* has been found to be strongly associated with type 2 diabetes in multiple studies. Several studies have suggested it also has a protective role against diabetic nephropathy^{80,81}. Likewise, variants near *KCNQ1*, which have been found to be associated with type 2 diabetes in Japanese patients, and subsequently other populations, was also associated with diabetic nephropathy⁸². A candidate gene study for the linkage region led to identification of a trinucleotide repeat in exon 2 of the *CNDP1* gene to be associated with diabetic nephropathy (OR 2.56, 95% CI 1.36–4.84)⁸³.

Other candidate gene studies have sought to examine the role of variants identified through GWAS for diabetic nephropathy in type 1 diabetes to explore their effects in type 2 diabetes. Analysis of four regions found to be associated with diabetic nephropathy in type 1 diabetes, namely 7p14.3, 9q21.32, 11p15.4 and 13q33.3, led to identification of the

11p15.4 locus (near *CARS*), and the 13q33.3 region as being associated with type 2 diabetes⁸⁴. In contrast, analysis of rs7583877 in *AFF3*, rs12437854 in the *RGMA-MCTP2* locus and rs7588550 in *ERBB4* in Japanese type 2 diabetes patients with nephropathy did not replicate the association previously observed in European patients with type 1 diabetes⁸⁵.

GWAS for Diabetic Nephropathy in Type 2 Diabetes

An early example that attempted to study genetic factors for diabetic nephropathy on a genome-wide scale was a Japanese study that investigated 50,000 gene-based polymorphisms. It identified the Arg913Gln substitution as within the solute carrier family membrane 3 (*SLC12A3*), a gene associated with Gitelman's syndrome, as being consistently associated with reduced risk of diabetic nephropathy⁸⁶. Another early example of genome-wide association study for diabetic nephropathy utilized a high-throughput system genotyping that combined the Invader assay with multiplex polymerase chain reactions, which provided genotyping for 81,315 SNP loci. This led to the identification of variants within the gene, *ELMO1*⁸⁷. Subsequent studies replicated the association of this SNP with diabetic nephropathy in African Americans⁸⁸, as well as in the Genetics of Kidney in Diabetes collection from the USA⁸⁹.

ELMO1 expression was markedly increased in the kidney of diabetic mice, especially in glomerular epithelial cells and tubular epithelial cells. Cells that overexpress *ELMO1* have increased expression of extracellular matrix protein genes, but decreased matrix metalloproteinases⁸⁷. Subsequent studies suggest *ELMO1* mediates development and progression of chronic glomerular injury through dysregulation of extracellular matrix metabolism⁹⁰.

A subsequent larger GWAS in the Japanese population identified *ACACB* (acetyl coenzyme A [CoA] carboxylase 2) at chromosome 12q24.1 as a susceptibility gene for diabetic nephropathy in type 2 diabetes. In this study, replication was sought in two additional Japanese cohorts, as well as other East Asians and a cohort from Denmark. *ACACB* encodes acetyl-CoA carboxylase beta, which catalyzes the carboxylation of acetyl-CoA to malonyl-CoA, thereby modulating fatty acid oxidation in the kidney. A significant association was not observed between this SNP and nephropathy in patients with type 1 diabetes⁹¹.

A meta-analysis of four studies from Japan found that the 13q region SNP, rs1411766, associated with nephropathy in type 1 diabetes was also associated with nephropathy in type 2 diabetes⁹². This study highlights the potential overlap in genetic factors for nephropathy in type 1 and type 2 diabetes, as well as potential consistent findings across different ethnic groups that would warrant further investigation using transethnic meta-analyses.

Despite the large number of variants in candidate genes identified to be associated with diabetic nephropathy, only a minority of these has been replicated in independent cohorts. In a meta-analysis of apolipoprotein E (ApoE) polymorphism

and diabetic nephropathy including 6,012 patients (with type 1 or type 2 diabetes) across 23 studies, the ApoE ϵ 2 allele was found to be associated with diabetic nephropathy with OR 1.64 (95% CI 1.26–2.13, $P = 0.00027$), and suggestive evidence of protection for the ApoE ϵ 4 allele⁹³. In a meta-analysis of replicated genetic factors for diabetic nephropathy, variants in several gene regions were consistently found to be associated with diabetic nephropathy. This included variants in or near *ACE*, *AKR1B1*, *APOC1*, *APOE*, *EPO*, *NOS3*, *HSPG2*, *VEGFA*, *FRMD3*, *CARS*, *CPVL/CN2*, *UNC13B* and *GREM1*⁷⁸.

Findings from GWAS for eGFR or CKD

Several loci have been identified through large-scale GWAS in European populations^{94,95}, as well as other populations^{96,97}. In the discovery cohort of one of the studies, diabetes was present in approximately 15–20% of study participants. In general, these novel variants for eGFR and CKD show minimal overlap with variants known to be associated with diabetic kidney complications. These variants did not overlap with regions associated with common causes of kidney disease, such as diabetes or hypertension, or many of the known pathways implicated in renal disease, such as the renin–angiotensin system, but instead implicate genes within the tubular compartment⁹⁸. Recently, the ability of these variants to predict incident CKD and ESRD has been tested in a general, mainly non-diabetic population of 26,308 individuals followed up for a median of 7.2 years, during which there were 2,122 cases of incident CKD. Interestingly, 11 of the 16 variants examined (*UMOD*, *PRKAG2*, *ANXA9*, *DAB2*, *SHROOM3*, *DACH1*, *STC1*, *SLC34A1*, *ALMS1/NAT8*, *UBE2Q2* and *GCKR*), were associated with incident CKD, with six remaining significantly associated after adjusting for baseline eGFR. Only very few of these SNPs were associated with incident ESRD⁹⁹. Although this study shows promise, the ability of these variants to predict deterioration of renal function in a population of patients with diabetes has not been examined.

ESRD in Diabetes

ESRD represents a severe phenotype that is closely related to diabetic nephropathy, and is usually defined as a combination of need for dialysis, renal transplantation or eGFR <15 mL/kg/m². It is worthwhile to note that studies have shown that patients with type 2 diabetes with diabetic nephropathy characterized by declined renal function and significant proteinuria are more likely to reach ESRD than die during 3-years follow up¹⁰⁰. Nevertheless, one should bear in mind that pathologies other than diabetic nephropathy could contribute towards development of ESRD in individuals with type 2 diabetes. Comparatively few studies have specifically used ESRD as the phenotype for examining diabetic kidney complications. A candidate gene study identified several variants within the *PRKCB1* gene to be associated with the development of ESRD in type 2 diabetes¹⁰¹. Variants in the gene, *PVT1*, have been identified to be associated with ESRD in both type 1 and type 2 diabetes,

with rs2648875 showing the strongest association with ESRD in type 2 diabetes^{102,103}. *PVT1* is co-amplified with the transcription factor, *MYC*, regulates cell cycle progression and is highly expressed in the kidney.

A recent study examined the role of 31 coding variants in 19 candidate regions for diabetic nephropathy in African American patients with type 2 diabetes and ESRD. Variants within *OR2L8*, *OR2AK2*, *C6orf167*, *LIMK2*, *APOL3*, *APOL2* and *APOL1* showed nominal association, with haplotype analysis of common and coding variants further improving the association signal for *OR2L13* and *APOL1* loci¹⁰⁴. The apolipoprotein L1 gene has been found to be strongly associated with non-diabetic ESRD among African Americans, as well as ESRD in patients with diabetes who are of African descent¹⁰⁵.

FROM GENETICS TO EPIGENETICS

In addition to genetic factors, there is increasing interest in the role of epigenetics in the pathogenesis of diabetes and diabetic complications. Epigenetics refer to the study of heritable, non-coding changes in the deoxyribonucleic acid that might impact on gene expression. Important epigenetic mechanisms that could modify gene expression include deoxyribonucleic acid methylation, histone modifications, microribonucleic acid (miRNA) and other non-coding RNAs. Epigenetics have become the focus of different research areas including gene–environment interaction, developmental origins of health and disease, as well as stem cell biology and cell differentiation. Epigenetic mechanisms have recently been implicated in the interaction of environmental factors, in particular hyperglycemia, with the development of vascular complications in diabetes^{106,107}. This is particularly relevant as a potential explanation of the phenomenon of glycemic memory, and the beneficial “legacy effect” of sustained improved metabolic milieu. Hyperglycemia have been shown to activate set-7 in vascular tissue, which provides a potential mechanism underlying glycemic memory¹⁰⁸. A study in the Finnish Diabetic Nephropathy Study cohort found an association between exonic genetic variants in *SUV39H1* histone methyltransferase gene within the set-7 pathway with the risk of nephropathy in patients with type 1 diabetes¹⁰⁹. Several pilot studies have been carried out to explore the role of epigenetic factors in diabetic nephropathy. For example, in a study that involved patients with type 1 diabetes and diabetic nephropathy, genome-wide methylation profiling using a methylation array identified 19 CpG sites with correlation to time-to-development of nephropathy, including one CpG site near the *UNC13B* gene, which ribonucleic acid had been implicated through earlier genetic studies¹¹⁰.

Another important epigenetic mechanism of gene expression regulation is through miRNAs. MiRNAs are a family of novel endogenous, small (approximately 22 nucleotides), single-stranded non-coding RNA molecules that play a major role in regulating post-transcriptional gene expression during development and other stages^{111,112}. MiRNAs act by having the 5' end

of the miRNA bind to the complementary target site at the 3' untranslated region of the target messenger RNA, thereby reducing gene expression. Several miRNAs, including miR-21, miR-192 and miR-93, have recently been implicated in diabetic nephropathy¹¹². Reduced circulating miR-126 have been reported in patients with type 2 diabetes¹¹³. A detailed discussion of the role of different miRNA is beyond the scope of the current review, and readers are referred to several excellent published reviews on this topic^{111,112,114}.

Several large-scale efforts are now underway to search for genetic and epigenetic markers related to diabetic complications^{115–118}. It is hoped that these efforts will identify new biomarkers for diabetic complications, and perhaps shed light on novel pathways in the pathogenesis of diabetic complications.

CONCLUSIONS

Although studies so far have identified a number of genetic variants associated with diabetic cardiovascular and renal complications, the number of variants associated with diabetic complications are rather limited compared with studies for genetic variants for type 2 diabetes or type 2 diabetes-related traits²⁴. This is partly related to the paucity of large well-characterized prospective studies to facilitate identification of genetic variants for diabetic complications. The current GWAS approach to the identification of genetic factors, although successful in identifying genetic polymorphisms with association to the disease of interest, are also limited by the inability to confer causality because of the difficulty in finding the causal functional variants. Resequencing studies will help to identify functional variants within identified regions. Finally, the need for large sample size of well-phenotyped subjects and the current costs associated with whole-genome genotyping or whole genome sequencing remain limitations for genetic studies, though these are likely to become less of a barrier in the near future as sequencing costs decrease.

Another major limitation of genetic studies in diabetic complications relate to the different definitions used and the difficulties relating to case ascertainment. As illustrated earlier, different definitions of diabetic kidney complications have been used, and in addition to different severity of coronary heart disease, there is the added difficulty relating to exclusion of underlying silent coronary disease among patients, especially with a long duration of diabetes. Given the interrelationship between diabetic cardiovascular and renal complications, future genetic studies should also consider the potential overlap between these complications in terms of their underlying pathogenesis.

Nevertheless, taking into account the differences in study design, case ascertainment and other methodological issues, findings across different ethnic groups for diabetic complications seem quite consistent. In the meta-analysis of genetic factors for diabetic nephropathy, meta-regression for variants that have been replicated in multiple ethnic groups (i.e., the *ACE* rs179975, *AKR1B1* CA repeat z-2, *APOE* 2/3/4 variant) and

ethnicity did not appear to explain the heterogeneity between different studies⁷⁸. As shown in Table 1, quite a few of the loci associated with diabetic kidney disease has also been replicated in different ethnic groups. Future studies utilizing trans-ethnic mapping might also help to narrow down functional variants within candidate gene regions identified through GWAS, as shown by the recent success utilizing this approach in studies of genetic variants for type 2 diabetes¹¹⁹. Current studies have yet to identify genetic factors that can explain the ethnic variation in the risk of diabetic renal complications¹²⁰. One potential explanation that has been invoked to explain the increased risk of renal complications in Asian patients is partly related to the reduced risk of cardiovascular disease, which could lead to amplification of renal disease prevalence as a result of competing mortality^{121,122}. The benefits of identifying novel genetic factors for diabetic complications could provide novel insights into disease pathogenesis, facilitate early identification of at-risk subjects and might provide novel strategies for intervention to reduce the burden of diabetic complications.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Reference list for Table 1.